

Conference: EESA Life in Space on Earth Symposium, University of Waterloo, Canada
Conference date: June 16-20, 2014
Web link: <http://www.congrexprojects.com/2014-events/14a07/introduction>
Abstract due: March 10, 2014

Focal gray matter plasticity as a function of long duration head-down tilt bed rest

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INTRODUCTION Long duration spaceflight (i.e., ≥ 22 days) has been associated with changes in sensorimotor systems, resulting in difficulties that astronauts experience with posture control, locomotion, and manual control. The microgravity environment is an important causal factor for spaceflight induced sensorimotor changes. Whether these sensorimotor changes may be related to structural and functional brain changes is yet unknown. However, experimental studies revealed changes in the gray matter (GM) of the brain after simulated microgravity. Thus, it is possible that spaceflight may affect brain structure and thereby cognitive functioning and motor behavior. Long duration head-down tilt bed rest has been suggested as an exclusionary analog to study microgravity effects on the sensorimotor system [1]. Bed rest mimics microgravity in body unloading and bodily fluid shifts. In consideration of the health and performance of crewmembers both in- and post-flight, we are conducting a prospective longitudinal 70-day bed rest study as an analog to investigate the effects of microgravity on the brain [2].

METHODS Ten subjects were assessed at 12 and 8 days before-, 7, 30, and ~70 days in-, and 8 and 12 days post 70 days of bed rest at the NASA bed rest facility at UTMB, Galveston, USA. At each time point high resolution T1-weighted MRI scans were obtained using a 3T Siemens scanner.

Focal GM volumetric changes over time were assessed using the voxel based morphometry 8 (VBM8) toolbox under SPM. Longitudinal processing in VBM8 includes linear registration of each scan to the mean of the subject and subsequently transforming all scans into MNI space by applying the warp from the mean subject to MNI, to the individual GM segmentations. Modulation was applied so that all images represented the volume of the original structure in native space. Finally, all images were smoothed. A flexible factorial model was used for voxel-wise, family-wise error corrected repeated measurement analysis of the VBM data.

Fully automated volume estimation of the GM of the frontal, temporal, parietal, and occipital lobe, the cerebellum, and the third and lateral ventricle was performed using the Brain Research Analysis of Images Networks and Systems (BRAINS) software package [3]. BRAINS uses an atlas-based anatomical identification procedure for the estimation of lobe volumes and ventricle volume, and applies an artificial neural network algorithm for cerebellar parcellation. A repeated measurements ANOVA was used to test the presence of significant changes in GM volume over time.

Functional mobility (FM) was tested 12 and 8 days pre-bed rest, the day subjects got out of bed, and 8 and 12 days post-bed rest. FM was tested using an obstacle course. Time needed to complete the FM test was the outcome measure. To take into account initial learning effects, we compared performance at 8 days pre-bed rest with performance the day subjects got out of bed using a paired sample t-test.

Brain-behavioral relationships were explored by correlating changes in focal and lobar GM with changes in FM.

RESULTS VBM analysis revealed a progressive decrease from pre- to in- bed rest in GM volume in bilateral areas including the frontal medial cortex, the insular cortex and the caudate. Over the same time period, there was a progressive increase in GM volume in the cerebellum, occipital-, and parietal cortex, including the precuneus. The majority of these changes did not fully recover during the post-bed rest period. Analysis of lobular GM volumes obtained with BRAINS showed significantly increased volume from pre-bed rest to in-bed rest in GM of the parietal lobe and the third ventricle. Temporal GM volume at 70 days in bed rest was smaller than that at the first pre-bed rest measurement. Trend analysis showed significant positive linear and negative quadratic relationships between parietal GM and time, a positive linear relationship between third ventricle volume and time, and a negative linear

relationship between cerebellar GM volume and time. FM performance improved from pre-bed rest session 1 to session 2. From the second pre-bed rest measure to the last-day-in-bed rest, there was a significant decrease in performance that only partially recovered post-bed rest. No significant association was observed between changes in brain volume and changes in functional mobility.

DISCUSSION Extended bed rest, which is an analog for microgravity, can result in local volumetric GM increase and decrease and adversely affect functional mobility. These changes in brain structure and performance were not related in this sample. Whether the effects of bed rest dissipate at longer times post-bed rest, and if they are associated with behavior are important questions that warrant further research including more subjects and longer follow-up times.

REFERENCES [1] Reschke MF et al. (2009) *Aviat Space Environ* 9; 80(5, Suppl.):A1–10. [2] Koppelmans V et al. (2013) *BMC Neurology* 13; 205. [3] Pierson R et al. (2011) *NeuroImage* 54; 328.

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